Health Center "Dr. Milenko Marin", Loznica[1]
University of Kragujevac, Faculty of Medical Sciences, Kragujevac
Department of Pharmacology[2]
University Clinical Center of Kragujevac, Kragujevac[3]

Original study
Originalni naučni rad
UDK 577.164.1:159.95
https://doi.org/10.2298/MPNS2210284L

DEFINING THE BREAKDOWN VALUE OF VITAMIN B12 AS AN IMPORTANT FACTOR IN THE DEVELOPMENT OF MILD COGNITIVE IMPAIRMENT

DEFINISANJE PRELOMNE VREDNOSTI VITAMINA B12 KAO ZNAČAJNOG FAKTORA U NASTANKU BLAGOG KOGNITIVNOG OŠTEĆENJA

Marija LAZAREVIĆ[1], Dragan MILOVANOVIĆ[2, 3] and Dejana RUŽIĆ ZEČEVIĆ[2, 3]

Summary

Introduction. The aim of our research is to determine the breakdown value of vitamin B12 in the blood that causes mild cognitive impairment. **Material and Methods.** Two hundred respondents participated in this research. Using screening tests, mild cognitive impairment was found in 50 patients, while in 150 patients the cognitive function was preserved. Borderline values and units of vitamin B12 concentration were determined according to the standards of the local laboratory and their reference values ranged from 138.00 to 652.00 pmol/l. **Results.** Using the t-test for independent samples, it was determined that there was a statistically significant difference in the values of vitamin B12 in relation to whether or not the respondents had mild cognitive impairment ($p = 0.000$), i.e. that respondents with mild cognitive impairment – 225.66 had significantly lower values of vitamin B12 than those without mild cognitive impairment – 421.06. The statistic analysis revealed that the area under the receiver operating characteristic curve was significantly above 0,5 (0.968) and this result was statistically significant ($p < 0.0005$). The breakdown value of vitamin B12 was determined as the maximum product between sensitivity and specificity. **Conclusion.** In this research, we determined that there was a statistically significant difference in the values of vitamin B12 in relation to whether or not the respondents had mild cognitive impairment. Being a significant risk factor for mild cognitive impairment, we defined the breakdown value of vitamin B12 which induces mild cognitive impairment of 300.5 pmol/l.

Key words: Vitamin B 12 Deficiency; Homocysteine; Cognitive Dysfunction; Signs and Symptoms; Risk Factors; Reference Values

Sažetak

Uvod. Cilj našeg istraživanja je utvrđivanje prelomne vrednosti nivoa vitamina B12 u krvi koja uzrokuje pojavu blagog kognitivnog oštećenja. **Materijal i metode.** U ovom istraživanju učestvovalo je 200 ispitanika. Pomoću skrining testova kod 50 pacijenata utvrđeno je blago kognitivno oštećenje, a 150 je bilo očuvane kognitivne funkcije. Granične vrednosti i jedinice koncentracije vitamina B12 određene su prema standardima lokalne laboratorije i njihove referentne vednosti kreću se od 138 do 652 pmol/l. **Rezultati**. Primenom t-testa za nezavisne uzorke utvrdili smo da postoji satistički značajna razlika u vrednostima vitamina B12 u odnosu na to da li ispitanici imaju ili ne blago kognitivno oštećenje ($r = 0,000$), odnosno da ispitanici koji imaju blago kognitivno oštećenje ($M = 225,66$) imaju značajno niže vrednosti od onih koji nemaju kognitivna oštećenja ($M = 421,06$). Statističkom analizom utvrđeno je da je površina ispod *receiver operating characteristic* krive znatno iznad 0,5 i iznosi 0,968 i ovaj rezultat je statistički značajan ($r < 0,0005$). Prelomna vrednost vitamina B12 određena je kao maksimalni proizvod između senzitivnosti i specifičnosti. **Zaključak**. U ovom istraživanju utvrdili smo da postoji satistički značajna razlika u vrednostima vitamina B12 u odnosu na to da li ispitanici imaju ili nemaju blago kognitivno oštećenje i kao značajan faktor rizika definisali smo prelomnu vrednost vitamina B12 kod ispitanika koja određuje pojavu blagog kognitivnog oštećenja i koja iznosi 300,5 pmol/l.

Ključne reči: deficit vitamina B12; homocistein; kognitivna disfunkcija; znaci i simptomi; faktori rizika; referentna vrednost

Introduction

It is known that vitamin B12 deficiency is a risk factor for cognitive impairment but it is not clear what the limit is, regarding a great range and influence of other factors. The level of vitamin B12 in blood for adult persons ranges from 200 - 600 pg/ml or 150 - 650 pmol/l, which may vary depending on the method by which it is determined.

Vitamin B12 (cyanocobalamin and hydroxocobalamin) is a compound which contains cobalt and in the body it turns into important coenzymes: methylcobalamin and deoxyadenosylcobalamin. The term cyanocobalamin is usually used for vitamin B12, because most of this substance enters the organism just in this form.

Researches have shown that vitamin B12 deficiency, besides hematological and gastrointestinal disorders, may lead to neuropsychiatric disorders and symptoms such as: neuropathy, cerebellar ataxia, dementia and mood disorders, occurring as a result of its insufficient intake, inadequate absorption or reduced usage. Accurate limit value which causes these disorders in an organism has not still been precisely defined.

Corresponding Author: Dr Marija Lazarevic, Dom zdravlja „Dr Milenko Marin",
15300 Loznica, Bolnička 65, E-mail: marijalazarevicsil@gmail.com

Abbreviations

MCI – mild cognitive impairment
ROC – receiver operating characteristic
HoloTC – holotranscobalamin
MMA – methylmalonic acid
Hcy – homocysteine
ALT – alanine transaminase
AST – aspartate aminotransferase

Cyanocobalamin participates in the metabolism of amino acids, regeneration of myelin and creation of bone marrow cells. Its deficiency causes degeneration of the lateral and dorsal columns of the spinal cord with consequent neuropathy. The cognitive dysfunction of these patients is often followed by irritability, depression, and in some cases psychoticism [1–3].

Neurological symptoms and disorders caused by the deficiency of vitamin B12 are various. In the nervous system, vitamin B12 acts as a coenzyme for L-methylmalonyl-CoA mutase which is necessary for the synthesis of myelin and thus its deficiency leads to myelin synthesis disorders. Vitamin B12 deficiency may cause combined neuropathy and myelopathy. The most frequent neurological manifestation of vitamin B12 deficiency is subacute combined degeneration caused by the degeneration/demyelination of lateral and dorsal columns of the spinal cord and neuropathy. The changes are most frequently seen in the cervical and thoracic areas, but they may occur in any part of the central nervous system except for the brain stem. The symptoms of neuropathy and medullopathy can appear separately or combined and they often precede the symptoms of anemia and cognitive dysfunction.

Cognitive dysfunction is manifested as mild cognitive impairment (MCI) or dementia. Vitamin B12 is important in the synthesis of S-adenosylmethionine, an important methyl donor in many reactions on the level of the central nervous system. Insufficient synthesis of S-adenosylmethionine can reduce the synthesis of monoamine neurotransmitters, and S-adenosylmethionine has an antidepressive function. The deficiency of vitamin B12 may present as episode of psychosis. Although such episodes are mostly seen in elderly and middle aged persons, psychotic episodes have also been described in adolescents [4, 5].

The clinical presentation may vary from behavior disorders, emotional distancing, psychomotor disorders, visual and audio hallucinations, insomnia, distrust and high levels of suspiciousness, believing things that are not based on reality, depression and anxiety, to suicidal thoughts. In persons with MCI, not all cognitive functions are impaired and they may not affect everyday functioning, thus they do not fulfill the main criteria for diagnosing dementia [6–8].

If MCI is established, it is necessary to determine its etiology, because timely diagnosis and determination of the main risk factors may lead to early and complete cure of the patient. One of the possible reasons for these symptoms is vitamin B12 deficiency which can be simply supplemented "per os" and by parenteral therapy [9–13].

The aim of our research was to determine the breakdown value of vitamin B12 in the blood that causes MCI.

Material and Methods

In this research we analyzed prospectively collected data by using methods of descriptive statistics and testing the hypothesis by t-test. Descriptive statistics included measures of central tendency and variability.

Two hundred respondents participated in the research. The following screening tests were used: mini-mental state examination (MMSE), Montreal cognitive assessment (MoCA) and Lawton instrumental activities of daily living (IADL) scale. Of 200 participants, MCI was found in 50 patients and 150 had a preserved cognitive function. In all the examinees, concentration of vitamin B12 in the serum was determined by using a routine method of clinical biochemistry, in an authorized laboratory of the Health Center. The limit values and units of concentration of vitamin B12 were determined by standards of the local laboratory. They were determined by taking blood samples and analyzing serum by chemiluminescent microparticle immunoassay (CMIA) (analyzer Abbot Alinity) and their reference value ranged from 138.00 to 652.00 pmol/l. This value was expressed as numerical continuous value.

To determine the cutoff value of vitamin B12 for determining MCI, we used the receiver operating characteristic (ROC) curve and the intersection of values based on the maximum product of sensitivity and specificity.

Results

The respondents were divided into two groups in regard to MCI. There were 50 respondents (25%) with MCI and 150 respondents (75%) in the control group without MCI.

The respondents were aged between 35 and 65 years, and the average age was 54.18 ± 5.90 years. The respondents in the study group were aged between 45 and 60 years, and the average age was 55.34 ± 3.85 years, while in the control group the respondents were aged between 35 and 65 years, and the average age was 53.79 ± 6.41 years.

The levels of vitamin B12 ranged from 73.8 to 1476.0, and the average level was 372.2 ± 153.1. The levels of vitamin B12 in the study group ranged from 73.8 to 326.6, and the average level was 229.9 ± 55.5, while in the control group the levels of vitamin B12 ranged from 198 to 1476, and the average level was 419.6 ± 145.8.

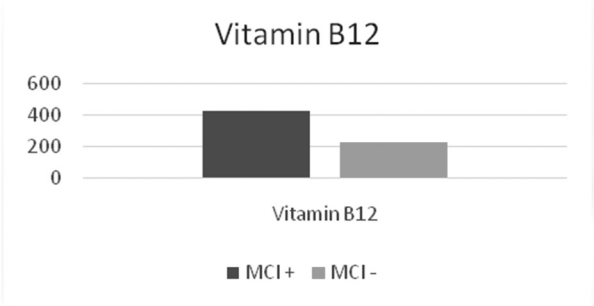
Among the respondents, there were 98 males (49%) and 102 females (51%). The study group included 24 males (48%) and 26 females (52%), while in the control group there were 74 males (49.3%) and 76 females (50.7%) **(Table 1)**.

By applying the t-test for independent samples, it was determined that there were statistically significant differences in the levels of vitamin B12 in respondents with and without MCI ($p = 0.000$). The respondents with MCI – 225.66 had significantly lower levels of vitamin B12 than those without MCI – 421.06 **(Graph 1)**.

Table 1. Descriptive statistics of the incidence of mild cognitive impairment in relation to gender and marital status
Tabela 1. *Deskriptivna statistika učestalosti blagog kognitivnog oštećenja u odnosu na pol i bračni status*

		All respondents/*Svi ispitanici*		MCI +/*BKO +*		MCI -/*BKO -*	
		No. *Broj*	Percentage *Procenat*	No. *Broj*	Percentage *Procenat*	No. *Broj*	Percentage *Procenat*
Sex *Pol*	Male/*Muško*	98	49	24	48	74	49.3
	Female/*Žensko*	102	51	26	52	76	50.7
Marrital status *Bračni status*	Unmarried *Nije u braku*	19	9.5	3	6	16	10.7
	Married/*U braku*	147	73.5	39	78	108	72
	Widowed/*Udovac*	34	17	8	16	26	17.3

Legenda: BKO – blago kognitivno oštećenje

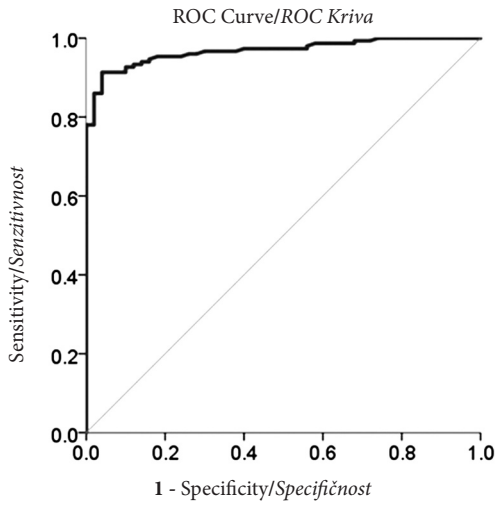


Graph 1. Level of vitamin B12 in the serum
Grafikon 1. *Nivo vitamina B12 u serumu*
MCI +* - Respondents with MCI)*/Ispitanici koji imaju* ***blago kognitivno oštećenje;* *MCI−*- Respondents without MCI*/Ispitanici koji nemaju blago kognitivno oštećenje*

The respondents with MCI had significantly lower levels of vitamin B12 than those wothout MCI. The breakdown value was determined as a maximum product between sensitivity and specificity **(Graph 2)**. The area below the curve was considerably above 0.5 and amounted to 0.968 and this result was statistically significant ($p < 0.0005$) **(Table 2)**. The breakdown value of vitamin B12, in order to establish MCI of the respondents, was 300.5 (approximate whole number was 300).

Discussion

Vitamin B12 deficiency due to insufficient intake, inadequate absorption and usability is an important risk factor for hematological, gastroenterological and neurological diseases. It is known that B12 deficiency leads to cognitive impairment. The aim of this study was to determine the limit value of B12 which predisposes cognitive impairment.



Graph 2. Maximum product of sensitivity and specificity
Grafikon 2. *Maksimalni proizvod osetljivosti i specifičnosti*

According to the European Food Safety Authority, the recommended adequate amount of vitamin B12 for adults is 4.0 μg/daily. Many scientists have been studying optimum levels of vitamin B12 in blood, as well as its bio-markers.

In the paper on the metabolism and concentration of vitamin B12, Obeid, R. et al. determined that the efficiency of vitamin B12 absorption from food was 40% and daily loss was between 2 and 6 μg/d, and daily intake of free cyanocobalamin of only 1.5 - 2.5 μg during approximately 4 - 6 months could increase vitamin B12 in plasma by 50 - 100 pmol/L [14, 15].

In a study including 98 Danish women in postmenopause, Bor et al. reported that the intake of 6 μg/d

Table 2. Sensitivity and specificity of vitamin B12 level
Tabela 2. *Osetljivost i specifičnost za nivo vitamina B12*

Area *Površina*	St. error *Std. greška*	p *p*	95% confidence interval/*95% interval poverenja*	
			Lower bound/*Donja granica*	Upper bound/*Gornja granica*
.968	.011	.000	.947	.989
Area under the curve/*Površina ispod krive*				
Test result variable(s): Level of vitamin B12 in the blood/*Varijabla(e) rezultata testa: nivo vitamina B12 u krvi*				

of vitamin B12 was sufficient for maintenance of the highest concentration of vitamin B12 and holotranscobalamin (holoTC), and the lowest concentration of methylmalonic acid (MMA) and homocysteine (Hcy) with median (25 - 75 percentile) of 380 (270 - 480) pmol/L for vitamin B12, 119 (92 - 162) pmol/L for holoTC, 0.12 (0.14 - 0.17) μmol/L for MMA and 9.8 (8.3 - 11.4) μmol/L for Hcy compared to the intakes lower than 6 μg/d [16]. A similar study including 299 healthy persons in the USA, found that the medium levels of vitamin B12 and holoTC were the highest in the ranges of intake between 4.2 and 7.0 μg/d, while the MMA and Hcy in plasma reached the lowest levels in subjects who achieved the intake of ≥ 7.0 μg/d.d [17].

In a meta-analysis on the association between the intake of vitamin B12 and biomarkers, Dullemeijer C. et al. estimated that doubling the intake of vitamin B12 was associated with higher concentration of vitamin B12 in serum. The difference in the change of vitamin B12 in plasma, regarding the intake of vitamin B12, was equal if the intake of vitamin B12 was > 100 μg/d, which could indicate limited proportional absorption of vitamin B12 from additional high doses [18].

In regard to the wide reference range, some researches point to the harmful effects of B12 high values. It has not been proved that high intake of B12 in food is harmful. Based on the evidence, additional forms of vitamin B12 are considered to be safe and there is no upper intake level of vitamin B12. However, increased concentrations of vitamin B12 in the plasma of persons who do not take additional vitamin B12 are described in studies including patients with various types of cancer, liver diseases or diabetes type 2, which were later attributed to kidney dysfunction [19, 20]. It was proved that clearance of one dose radioactively marked vitamin B12 was stored in patients with kidney dysfunction [21]. The studies conducted in hospital conditions showed that the increased level of vitamin B12 in plasma is associated with increased levels of liver enzymes and creatinine or albuminuria [22] as well as several clinical conditions such as kidney diseases, diabetes, liver disorders (of any etiology), alcoholism or malignancy [23, 24].

The causes of vitamin B12 deficiency and its consequential clinical manifestations, which affect cognition, include a wide spectrum of pathological conditions: reduced intake of vitamin B12 due to stomach pathology, bowel diseases, inborn selective malabsorption of vitamin B12 with proteinuria, chronic pancreatitis, malabsorption caused by medications, in increased needs of a body during pregnancy, hyperthyroidism and presence of tumors [25–28].

The disorders associated with using vitamin B12 play equally important role in vitamin B12 deficiency, like reduced absorption, although these are rare causes. These disorders include inborn deficiency of transcobalamin, with homocystinuria and inborn intrinsic factor deficiency.

Mild cognitive impairment is the intermediate stage between the cognitive changes of normal aging and very early dementia. It is a disorder which precedes dementia and in many persons it causes memory disorders which are mild and do not disable everyday independent functioning, but they are still inappropriate for the patient's age and education. It has been proved in many researches that MCI can be caused by deficiency of vitamin B12.

A high level of homocysteine in blood (hyperhomocysteinemia) is a risk factor for diseases in which metabolism depends on B vitamins. The use of vitamin B12 can reduce the risk of dementia. The vitamin B12 deficiency becomes relevant when cobalamin participates in formation of purine and pyrimidine, affecting cell duplication, in the way that these processes can cause neurological and psychiatric diseases including cognitive impairments and dementia. This can lead to deterioration of subcortical damages which are sometimes reversible and if they are recognized in early phases, the deficiency can be restituted. Cyanocobalamin use has shown favorable outcomes in various clinical and epidemiological studies. The question is, what are the limit values for vitamin B12 deficiency that can be tolerated by an organism, i.e. that do not lead to cognitive impairment and other clinical manifestations.

Vitamin B12, together with vitamin B6 and folic acid, can reduce high doses of homocysteine in blood. The deficiency of vitamin B leads to low enzyme activities for remethylation of homocysteine into methionine. The results of inefficient reaction of methylation contributes to the development of heart diseases, osteoporosis, Parkinson's disease and Alzheimer's disease. Vitamins B are necessary in the synthesis of S-adenosyl methionine and for methylation of deoxyribonucleic acid. Methylation is a key mechanism by which a body deals with toxins, stress and infections.

Between April and October of 2016, a case-control study was conducted in which the Spearman's correlation analysis showed that homocysteine has an important positive correlation with alanine transaminase (ALT) and aspartate aminotransferase (AST), while a negative correlation was determined between homocysteine, Mini-mental status examination score, Wechsler Adult Intelligence Scale - revised by China intelligence quotient, folate and vitamin B12. Lower levels of folates and hiher levels of Hcy and ALT and AST were associated with the risk of MCI. Higher levels of ALT, AST, Hcy and lower levels of folates were independently related to the risk of MCI [29].

Hyperhomocysteinemia is an independent risk predictor of cognitive decline and can be the result of low level of vitamins B12, B6 and folates, while adequate intake of these vitamins can reduce the levels of homocysteine.

A review study of Olaso G. G. et al. aimed to estimate the effects of vitamins B6, B12 and/or folic acid on the levels of homocysteine in patients with MCI. This review showed that the level of homocysteine in plasma of patients with MCI who were taking vitamins B6, B12 and/or supplements of folic acid was reduced and a statistically significant fall was noticed after 1 month of taking supplements. The results confirm that taking supplements of these vitamins may be the option for reducing the level of homocysteine in persons with MCI and higher homocysteine in the plasma [30].

Homocysteine is a risk factor for brain atrophy, cognitive impairments and dementia. Vitamin B12 and folate are necessary for the methylation of Hcy that is a risk factor for brain atrophy, cognitive impairments and dementia.

The study of Fei Ma et al. estimated how the levels of Hcy in the plasma and its biological determinants, folates and vitamin B12 are associated with MCI and Alzheimer's disease in the elderly Chinese population. Low level of folates and vitamin B12 in blood and higher levels of Hcy were connected to MCI and Alzheimer's disease in the elderly Chinese population and the connection was stronger for Alzheimer's disease [31].

The research conducted by Stanetić K. et al. showed that patients with cognitive impairment and dementia are not fully capable of independent functioning due to the frequency of falls. They pointed out the importance of preventing cognitive impairment [32].

Conclusion

In this case-control study, we determined the levels of vitamin B12 in two groups of respondents: a group with and a group without mild cognitive impairment. By applying the t-test for independent samples, we determined that there was a statistically significant difference in levels of vitamin B12 in respondents with and respondents without mild cognitive impairment. As an important risk factor, we defined the breakdown value of vitamin B12 which is associated with the occurrence of mild cognitive impairment of 300.5 pmol/l.

References

1. Kirin S. Neurološke smetnje usled manjka vitamina B12 [diplomski rad]. Rijeka: Sveučilište u Rijeci, Medicinski fakultet; 2016.
2. Hesdorffer CS, Longo DL. Drug-induced megaloblastic anemia. N Engl J Med. 2015;373(17):1649-58.
3. Teigen LM, Twernbold DD, Miller WL. Prevalence of thiamine deficiency in a stable heart failure outpatient cohort on standard loop diuretic therapy. Clin Nutr. 2016;35(6):1323-7.
4. Chauhan K, Agarwal A. Vitamin B12 supplementation and cognitive scores in geriatric patients with mild cognitive impairment. Functional Foods in Health and Disease. 2016;6(9):578-86.
5. Canevelli M, Remoli G, Toccaceli Blasi M, Tariciotti L, Sarli G, Valletta M, et al. Ongoing research protocols for the pharmacological treatment of neuropsychiatric symptoms in dementia. J Frailty Aging. 2021;10(1):22-30.
6. Pavlović DM, Pavlović AM, Totić S. Farmakoterapija demencija. Vojnosanit Pregl. 2010;67(5):419-26.
7. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005;366(9503):2112-7.
8. Salloway S, Correia S. Alzheimer disease: time to improve its diagnosis and treatment. Cleve Clin J Med. 2009;76(1):49-58.
9. Giacobini E. Cholinesterase inhibitor therapy stabilizes symptoms of Alzheimer disease. Alzheimer Dis Assoc Disord. 2000;14 Suppl 1:S3-10.
10. Urbanski G, Villoteau A, Lozac'h P, N'guyen M, Schlumberger E, Beucher AB, et al. Carence en vitamine B12, metformine et inhibiteurs de pompe à protons. La Revue de Médecine Interne. 2017;38(Suppl 2):54-5.
11. Aroda VR, Edelstein SL, Goldberg RB, Knowler WC, Marcovina SM, Orchard TJ, et al. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab. 2016;101(4):1754-61.
12. Miller JW. Proton pump inhibitors, H2-receptor antagonists, metformin, and vitamin B-12 deficiency: clinical implications. Adv Nutr. 2018;9(4):511S-8.
13. Huang HL, Zhou H, Wang N, Yu CY. Effects of antiepileptic drugs on the serum folate and vitamin B12 in various epileptic patients. Biomed Rep. 2016;5(4):413-6.
14. Obeid R, Heil SG, Verhoeven MMA, van den Heuvel EGHM, de Groot LCPGM, Eussen SJPM. Vitamin B12 intake from animal foods, biomarkers, and health aspects. Front Nutr. 2019;6:93.
15. van de Lagemaat EE, de Groot LCPGM, van den Heuvel EGHM. Vitamin B12 in relation to oxidative stress: a systematic review. Nutrients. 2019;11(2):482.
16. Bor MV, Lydeking-Olsen E, Moller J, Nexo E. A daily intake of approximately 6 microg vitamin B-12 appears to saturate all the vitamin B-12-related variables in Danish postmenopausal women. Am J Clin Nutr. 2006;83(1):52-8.
17. Bor MV, von Castel-Roberts KM, Kauwell GP, Stabler SP, Allen RH, Maneval DR, et al. Daily intake of 4 to 7 microg dietary vitamin B-12 is associated with steady concentrations of vitamin B-12-related biomarkers in a healthy young population. Am J Clin Nutr. 2010;91(3):571-7.
18. Dullemeijer C, Souverein OW, Doets EL, van der Voet H, van Wijngaarden JP, de Boer WJ, et al. Systematic review with dose-response meta-analyses between vitamin B-12 intake and European Micronutrient Recommendations Aligned's prioritized biomarkers of vitamin B-12 including randomized controlled trials and observational studies in adults and elderly persons. Am J Clin Nutr. 2013;97(2):390-402.
19. Chow BF, Rosen DA, Lang CA. Vitamin B12 serum levels and diabetic retinopathy. Proc Soc Exp Biol Med. 1954;87(1):38-9.
20. Halsted JA, Carroll J, Rubert S. Serum and tissue concentration of vitamin B12 in certain pathologic states. N Engl J Med. 1959;260(12):575-80.
21. Beckett AG, Matthews DM. Vitamin B12 in diabetes mellitus. Clin Sci. 1962;23:361-70.
22. McMahon GM, Hwang SJ, Tanner RM, Jacques PF, Selhub J, Muntner P, et al. The association between vitamin B12, albuminuria and reduced kidney function: an observational cohort study. BMC Nephrol. 2015;16(1):7.
23. Brah S, Chiche L, Mancini J, Meunier B, Arlet JB. Characteristics of patients admitted to internal medicine departments with high serum cobalamin levels: results from a prospective cohort study. Eur J Intern Med. 2014;25(5):e57-8.
24. Carmel R, Vasireddy H, Aurangzeb I, George K. High serum cobalamin levels in the clinical setting – clinical associations and holo-transcobalamin changes. Clin Lab Haematol. 2001;23(6): 365-71.
25. Arendt JF, Sorensen HT, Horsfall LJ, Petersen I. Elevated vitamin B12 levels and cancer risk in UK primary care: a THIN database cohort study. Cancer Epidemiol Biomarkers Prev. 2019;28 (4):814-21.

26. Willett W, Rockstrom J, Loken B, Springmann M, Lang T, Vermeulen S, et al. Food in the Anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. Lancet. 2019;393(10170):447-92.

27. Schupbach R, Wegmuller R, Berguerand C, Bui M, Herter-Aeberli I. Micronutrient status and intake in omnivores, vegetarians and vegans in Switzerland. Eur J Nutr. 2017;56(1):283-93.

28. Alles B, Baudry J, Mejean C, Touvier M, Peneau S, Hercberg S, et al. Comparison of sociodemographic and nutritional characteristics between self-reported vegetarians, vegans, and meat-eaters from the NutriNet-Sante Study. Nutrients. 2017;9(9):1023.

29. Zhou X, Wang Q, An P, Du Y, Zhao J, Song A, et al. Relationship between folate, vitamin B12, homocysteine, transaminase and mild cognitive impairment in China: a case-control study. J Food Sci Nutr. 2020;71(3):315-24.

30. Olaso-Gonzalez G, Inzitari M, Bellelli G, Morandi A, Barcons N, Viña J. Impact of supplementation with vitamins B6, B12, and/or folic acid on the reduction of homocysteine levels in patients with mild cognitive impairment: a systematic review. IUBMB Life. 2022;74(1):74-84.

31. Ma F, Wu T, Zhao J, Ji L, Song A, Zhang M, et al. Plasma homocysteine and serum folate and vitamin B12 levels in mild cognitive impairment and Alzheimer's disease: a case-control study. Nutrients. 2017;9(7):725.

32. Stanetić K, Kević V, Stanetić M. Effects of depression and dementia on the risk of falls in elderly treated at the Health Center Banja Luka. Med Pregl. 2018;71(11-12):368-76.

Rad je primljen 18. XI 2022.
Recenziran 25. II 2023.
Prihvaćen za štampu 1. III 2023.
BIBLID.0025-8105:(2022):LXXV:9-10:284-289.